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Laure L. Grandin, Laurent L. Orsi, Xavier X. Troussard, Alain A. Monnereau, Christian C. Berthou, Pierre P. Fenaux, Gerald G. Marit, Pierre Soubeyran, Françoise F. Huguet, Noël N. Milpied, et al.

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UV RADIATION EXPOSURE, SKIN TYPE AND LYMPHOID MALIGNANCIES: RESULTS OF A FRENCH CASE-CONTROL STUDY.

Grandin L[1,2], Orsi L[1,2], Troussard X[3], Monnereau A[1,2,4], Berthou C[5], Fenaux P[6], Marit G[7], Soubeyran P[4], Huguet F[8], Milpied N[9], Leporrier M[3], Hemon D[1,2], Clavel J[1,2].

Authors' affiliations:

[1] INSERM, U754, F-94800 Villejuif, France

[2] Paris-Sud University, UMR-S754, IFR69, F-94800 Villejuif, France

[3] Côte de Nacre Hospital, Caen, France

[4] Bergonié Institute, Comprehensive cancer center, Bordeaux, France

[5] Morvan Hospital, Brest, France

[6] Avicenne Hospital, Bobigny, France

[7] Haut-Lévêque Hospital, CHU Bordeaux, Pessac, France

[8] Purpan Hospital, Toulouse, France

[9] Hôtel Dieu Hospital, Nantes, France

Correspondence to:

Dr. Jacqueline Clavel

Inserm U754

16, av. Paul Vaillant-Couturier

F-94807 VILLEJUIF Cedex

Tel.: 33 1 45 59 50 38 /50 37

Fax: 33 1 45 59 60 20

Mail: clavel@vjf.inserm.fr

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Abstract:

Objectives Investigating the relationship between skin type, UV exposure and lymphoid malignancies (LM).

Methods We conducted a hospital-based case-control study in France, including 813 incident cases of non-Hodgkin's lymphoma (NHL), Hodgkin's lymphoma (HL), lymphoproliferative syndrome (LPS) or multiple myeloma and 748 controls.

Results Positive associations between HL and blond/red hair (OR=1.8 [0.8-3.8]), very fair/fair skin (OR=1.6 [1.0-2.5]) were observed. High propensity to burn was associated with HL (OR=1.5 [1.0-2.2]) and LPS (OR=1.4 [1.0-2.1]). Poor ability to tan was significantly associated with HL (OR=1.7 [1.0-2.8]). Having light hair with high propensity to burn was associated with NHL (OR=1.5 [0.9-2.5]) and significantly with HL (OR=3.4 [1.4-8.4]). Having dark hair with high propensity to burn was significantly associated with LPS (OR=1.5 [1.0-2.0]). The associations with HL and NHL were significant for men only, with significant interactions. Outdoors activities since leaving school or in the last decade were not related to LM. Only an almost negative trend was observed. Prior exposure to artificial UV was not associated with LM.

Conclusion These results suggest a positive association between the most reactive and palest skin types and NHL or HL in men and do not rule out a slight negative relationship between UV exposure and LM.

Key words: epidemiology; lymphoma; skin type; UV radiation exposure; case-control study

INTRODUCTION

The hypothesis that solar UV radiation might explain the worldwide increase in the incidence of non-Hodgkin's lymphomas (NHL) over the preceding thirty years was first suggested in 1992 (1). In support of that hypothesis, Cartwright et al. (2) reported worldwide geographic and temporal correlations between the incidence of skin cancer and NHL (44 cancer registries, cancer incidence in five continents, 1956-62 and 1978-82). Exposure to UV radiation increased over the same period in all the industrialized countries and is the principal known risk factor for skin cancer. Cartwright also noted that NHL incidence had increased in several populations considered to be particularly exposed to UV radiation (farmers, white Vietnam veterans, Australian immigrants). In addition, studies conducted on humans and animals showed that UV radiation exposure induced systemic immune suppression (3), which is one of the greatest known risk factors for NHL (4) and other lymphoid malignancies (LM).

Hu et al (2005) reviewed the registry-based cohort studies and showed that they all reported an increased risk of NHL after a first skin cancer, or, conversely, an increased risk of skin cancer after NHL (5), which suggests common etiologic factors. In three European ecological studies (6-8), the risk of NHL increased with decreasing latitude or with increasing UV index. Two studies, in Sweden and the USA (9,10), found a non-significant positive association between high occupational sun exposure and the risk of NHL in men. A large population-based case-control study (11) identified a direct, weak, significant, positive association between the palest skin types and the risk of NHL in Australia.

In contrast, some studies have evidenced inverse relationships between high UV radiation exposure and the risk of LM. In five North American ecological studies (12-17), the risk of NHL decreased with decreasing latitude or with increasing UV radiation index. Two studies, in Sweden and the USA (8,14), found a significant negative association between occupational sun exposure and the risk of NHL. Three large population-based case-control studies (18-20) evidenced significant negative associations between different indices of intermittent UV radiation exposure and the risk of NHL, CLL and Hodgkin's lymphoma (HL) in Australia, Sweden, Denmark and Germany. A recent population-based case-control study in the USA reported similar results for chronic or intermittent UV radiation exposure, although the associations were not significant (21). Vitamin D synthesis may be involved in the protective effect of sun exposure with regard to LM (22,23).

This study investigated the role of skin type and UV radiation exposure with respect to the main groups of LM in France.

MATERIALS AND METHODS

Subjects

A hospital-based case-control study was carried out in the French cities of Bordeaux, Brest, Caen, Lille, Nantes and Toulouse from September 2000 to December 2004. The hospital-based design of the study was chosen to address the need for case and control blood samples, according to the French ethical regulation at the time the study was conducted. Eligible cases were subjects aged 20-75 years, presenting with recently-diagnosed, cytologically- or histologically-confirmed LM, living in the the hospital's geographical area. All the diagnoses were reviewed by a panel of pathologists and hematologists. Patients with a history of immunosuppression for organ transplantation or a history of HIV infection were not eligible. Of the 872 subjects eligible during the recruitment period, 48 (5.5%) refused to participate. For this paper, 11 cases of non-Caucasian or unknown ethnic origin were excluded (5 North Africans, 2 Africans, 2 West Indians, 1 Asian and 1 subject of unknown ethnic origin). In all, 813 cases were included in the analysis. The cases were classified using the ICD-O classification, 3rd revision. The study sample included 395 cases of NHL (170 cases of diffuse large B-cell lymphoma (DLCL) (9679/3, 9680/3), 101 of follicular lymphoma (FL) (9690/3, 9691/3, 9695/3, 9698/3), 21 of lymphoplasmacytic lymphoma/Waldenstrom macroglobulinemia (9671/3, 9761/3), 17 of marginal zone B-cell lymphoma of MALT type (9699/3), 3 of splenic marginal zone B-cell lymphoma (9689/3), 25 of T-cell lymphoma (9702/3, 9705/3, 9714/3, 9729/3), 24 of mantle-cell lymphoma (9673/3) and 34 of other lymphoma (9728/3, 9687/3, 9826/3, 9591/3)), 147 cases of HL (103 of nodular sclerosis-type HL (9661-9665/3, 9667/3), 44 of other HL (9650-9655/3, 9659/3), 168 cases of lymphoproliferative syndrome (LPS) (132 of CLL (9823/3, 9670/3), 36 of hairy cell leukemia (HCL) (9940/3)), and 103 cases of multiple myeloma (MM) (9731/3, 9732/3).

The controls were patients with no prior history of hematological neoplasm recruited in the same hospitals as the cases, mainly in orthopedic and rheumatologic departments and living in the hospital's geographical area. Subjects admitted for cancer, or a disease directly related to occupation, smoking or alcohol abuse were not eligible to be controls, in order to avoid overrepresentation of some of the factors of interest. The controls were individually matched with the cases by center, age (± 3 years) and gender. The aim of the matching was to ensure that at least one control would be available for each case. Out of the 853 controls ascertained and initially confirmed as eligible, 100 (11.7%) refused to participate. Four non-Caucasian controls were excluded (2 North Africans, 1 West Indian and 1 subject of unknown ethnic origin). A further control whose interview was incomplete was also excluded. In all, 748 controls were included in the analysis. The reasons for hospital admission were mainly orthopedic or rheumatologic (fractures (19.9%), wounds (0.9%), other non-occupational injuries (10.7%), osteoarthritis (23.2%), back diseases (15.4%), polyarticular diseases (4.0%), infectious bone and joint diseases (2.9%), minor musculoskeletal malformations (4.8%), other diseases of the bones and joints (7.2%)), peripheral nervous disorders (2.1%), digestive, urinary or genital tract diseases (4.8%), cardiovascular diseases (1.3%), skin and subcutaneous tissue diseases (2.0%), and infections (0.8%).

Data collection

Except for the LPS cases, who could be included up to 18 months post-diagnosis because of the good prognosis, all the cases were to be recruited within 6 months of diagnosis. Most (89.3%) were included within 3 months (median: 42 days).

Data collection was conducted in two stages. The patients first completed a standardized self-administered questionnaire on their occupational, familial and residential histories. They were then interviewed using a structured, standardized questionnaire by trained interviewers not aware of the hypotheses under study. The questions addressed medical history of infections, immunization and chronic diseases, pigmentary characteristics, skin reaction to the sun, outdoor leisure activities, sunlamp and sun bed use, lifestyle and a list of occupational exposures. The latter list and the self-administered occupational questionnaire were reviewed with the patients by the interviewers, and *ad hoc*, standardized, specialized, occupational questionnaires (e.g. farmers, textile workers, mechanics, painters, launderers) were administered.

Biological specimens

Biological specimens (serum, plasma, DNA, RNA and tumoral tissue) were obtained from the cases and controls with their informed consent. A DNA bank was constituted.

Variables analyzed

Socioeconomic category

The socioeconomic category was determined on the basis of the last job held and encoded using the international classification of the International Labor Office (1968 revision). Educational level was also used as a marker of social category.

Pigmentary characteristics and sensitivity to the sun (skin types)

Pigmentary characteristics were evaluated using structured questions on eye color (albino, blue/grey, green, hazel, brown/black), youthful natural hair color (blond, red, light brown/dark brown, black) and skin color on the medial upper arm before any UV exposure (albino, very fair, fair, olive, brown). The propensity to burn was evaluated by the skin reaction to the first unprotected seasonal sun exposure (severe burn with blisters, painful burn then peel, burn then tan, tan without burning). The ability to tan was evaluated by the skin reaction to repeated exposures to the sun (no tan, mild tan, moderate tan, deep tan). In this article, those characteristics constitute the skin type. A combined variable was constructed from the variables available in the questionnaire that seemed to summarize the phototype best, given their observed distribution in the sample. Thus, hair color and propensity to burn were combined in a "hair and skin profile" variable with 3 categories: (1) light hair (blond/red) and sensitive skin (severe/painful burn) (2) dark hair (light brown/dark brown/black) and sensitive skin (severe/painful burn) (3) not sensitive skin (burn then tan/tan without burning).

Exposure to sun and artificial UV light

Sun exposure was assessed in terms of outdoor leisure activities since leaving school until the interview or in the decade before the interview. The history of regular outdoor activities practiced by day (9 am to 5 pm) since the end of school was collected through closed questions. Water sports, snow sports, ball gaming, racquet sports, hiking, walking, running, cycling and others as well as gardening or sunbathing were considered as outdoor leisure activities. The frequency (hours per year) and duration of exposure were elicited for each activity. The weekly duration of outdoor activities was divided into quartiles and the lowest quartile of exposure (>0 and ≤ 1hour/week) was pooled with the unexposed category.

Artificial UV light exposure was assessed by questions about the use of sun beds or sunlamps for esthetic or therapeutic purposes and the medical reason for treatment was requested for UV therapy. The frequency of exposure and times of the first and last exposures were elicited.

Study power

For NHL, with power of 80% and a two-sided alpha error of 5%, the size of the study sample was sufficient to evidence ORs of about 1.5 or 0.7 for most of the subject characteristics, 1.6 or 0.6 for the highest quartile for outdoor leisure activities, and 1.9 or 0.5 for exposure to artificial UV. For HL, LPS and MM, ORs of about 2.0 or 0.4 could be evidenced for the same variables.

Statistical analysis

The pair-matching used as a basis for the recruitment was broken to allow the use of the whole control group for the analysis of all LM types, with stratification by age (5-year age groups), gender and center. For each subgroup, HL, NHL, LPS and MM, the cases and controls were grouped into the age, gender and center strata. Strata with no cases were excluded, so that, in the unconditional analyses by subgroups, only controls who could be included in one of the strata covered by the corresponding subgroup of cases were considered.

After having checked the comparability of the cases and controls with respect to the matching variables (age, gender and center) and socioeconomic categories, each variable of interest was analyzed alone using unconditional logistic regression models including the stratification variables. The relationships were analyzed by histological type (NHL, HL, LPS and MM) and by gender. Variables were studied jointly in multivariate regressions and the interactions between variables were tested. Occupation as farmer and a history of mononucleosis were considered as possible confounders in the analysis (24,25).

To test the stability of the results, analyses were performed by excluding in turn from the analysis each center strata, on the one hand, and each group of controls with the same diagnosis, on the other hand. Analyses were also conducted using conditional logistic regression models.

All the analyses were implemented using SAS software V 9.1 (SAS institute, Cary NC., 1989).

The study protocol was submitted to the CNIL (90003) and DGS (2000/0107) for data privacy and ethical approval.

RESULTS

Subject characteristics

The distribution of the cases and controls by stratification variable is shown in table 1. Use of the whole control group assigned more than 2 controls to each case in most strata, except in the youngest categories, in which HL predominated, and the ages of the cases and controls therefore differed significantly. The MM cases differed from the controls with regard to gender since they did not show the male predominance observed in other lymphoid malignancies. Lastly, significant differences were also observed for the centers, mainly because the Caen hospital had a higher LPS recruitment than the other centers.

The 'farmers' category was more frequent in the NHL and MM cases than in the controls. The HL cases were less often in the lowest socioeconomic categories than the controls (OR = 0.5 [0.3-0.9]) (table 1).

Pigmentary characteristics and sensitivity to the sun (skin types)

The associations between skin types and LM are shown in table 2. LPS cases slightly more frequently had blue, gray or green eyes than controls. Positive but non-significant associations between HL and blond or red hair (OR = 1.8 [0.8-3.8]) and between HL and very fair or fair skin color (OR = 1.6 [1.0-2.5]) were observed.

A strong reaction to the first unprotected seasonal sun exposure (severe burn with blisters or painful burn with peeling) was positively, but not significantly, associated with HL (OR = 1.5 [1.0-2.2]) and LPS (OR = 1.4 [1.0-2.1]). The ability to tan with repeated exposures to the sun was also significantly associated with HL. The HL cases tended not to get tanned or get mildly tanned more often than the controls (OR = 1.7 [1.0-2.8]).

With regard to the combination of hair color and propensity to burn during the first seasonal sun exposure, having blond or red hair and experiencing severe or painful sunburn from the first seasonal sun exposure was significantly associated with HL (OR = 3.4 [1.4-8.4]) and non-significantly with NHL (OR = 1.5 [0.9-2.5]). Having light brown, dark brown or black hair and experiencing severe or painful sunburn from the first seasonal sun exposure was significantly associated with LPS (OR = 1.5 [1.0-2.0]).

The associations observed with HL and NHL were significant for men but not for women, with significant interactions between gender and hair color for NHL (p = 0.03) and between gender and propensity to burn for HL (p = 0.04). For NHL and for men, these associations are based on 23 cases for light hair color, 163 cases for light skin color, 115 cases for high propensity to burn, 33 cases for low ability to tan, 21 cases for light hair color with sensitive skin and 94 cases for dark hair color with sensitive skin. For HL and for men, the number of cases was 7, 66, 45, 13, 7 and 38 respectively. No interaction with gender was observed for the other LM.

When subgroups were considered, similar results were observed for DLCL and FL (results not shown). Strong sensitivity to the first seasonal exposure to sun and a poor ability to tan were both significantly associated with hairy cell leukemia (HCL).

Exposure to sun and artificial UV light

Overall, outdoor activities were not related to LM. Restricting exposure to the last decade did not evidence any relationship. Only an almost negative trend was observed, with ORs less than the unity (table 3). Prior exposure to artificial UV light, i.e. sun beds or sunlamps for esthetic or medical reasons, was not associated with any LM.

Stability of the results

The associations remained unchanged when each category of control disease or each center was excluded, one by one. Adjustments for socioeconomic category, farming, education and history of mononucleosis did not change the results. The results generated by conditional analyses were similar. Mutual adjustment for skin type, sun exposure through outdoor activities and artificial UV radiation exposure did not change the results.

DISCUSSION

The main findings of the study were the significant association of both NHL and HL with the skin types considered most sensitive to sun exposure (i.e. blond or red hair with the highest propensity to burn on the first seasonal sun exposure) for men. An association was observed for DLCL and FL. Weaker associations were observed for LPS. Outdoor leisure activities since leaving school or in the preceding decade were not associated with any type of malignant lymphoma. Only an almost negative trend was observed, with ORs less than the unity.

The study was hospital-based because blood samples were required. The cases and controls were drawn from the same population. Recruitment was restricted to cases and controls living in the hospital catchment area in order to avoid the selection of cases from a population better informed and receiving better care than the population recruited from the control departments. Only 5.5% of the contacted cases refused the interview and all the eligible cases admitted to the hospital departments during the study period were contacted. The cases are therefore likely to be representative of all the cases in that population. In addition, the non-Caucasian cases and controls included in the study were excluded from the analyses. Therefore, there is no particular reason for the selection process having overrepresented cases with blond or red hair or underrepresented those with brown or black hair due, for instance, to socioeconomic characteristics related to particular ethnic origins. A survival bias could have occurred if the skin type and reaction to sun exposure were related to the seriousness of the disease or to the response to treatment. In order to avoid selection by survival, only incident cases were recruited shortly after diagnosis.

The controls were recruited in the same hospitals as the cases, and contemporaneously, from departments which were assumed not to select particular populations. The inclusion of patients admitted for diseases directly related to alcohol abuse, smoking or occupation could have lead to an overrepresentation of the lowest socioeconomic categories. The patients were therefore mainly recruited patients admitted to orthopedic or rheumatologic departments for various reasons. The initial age, gender and center matching ensured the comparability of cases and controls. Except for HL, the cases and controls belonged to similar socioeconomic categories. The higher socioeconomic category for HL is unlikely to reflect selection of less wealthy controls since it has already been reported in several studies (26). It is not easy to determine whether control selection may have overrepresented subjects more likely to have outdoor activities, present with a particular phototype, or have a low vitamin D level. So doing might have masked a relationship. However, when each type of control disease or each center was excluded one by one, the results were similar. Moreover, comparable estimates were generated by the unconditional and conditional analyses, although, in the latter, the control group was not shared by the various groups of cases.

The association between skin type and risk of NHL and HL was only found in men. Male and female controls were admitted to the same departments for the same diseases. There is thus no obvious clue with regard to a potential bias that may explain the finding. Overall, among the controls, the women were more often blond and fair than the men, which could have masked a relationship if the discrepancy was due to a particular selection. However, the distribution by gender of skin and hair colors in the control group is the same as that in the SU.VI.MAX survey, carried out on a representative sample of the French population (27).

All the cases were documented and the diagnoses were reviewed by a panel of pathologists and hematologists before classification. Thus, the similarity of the results for the lymphoma subgroups is unlikely to be due to diagnostic misclassification.

The questionnaire was standardized and administered to the cases and controls in a given center by the same interviewers. The latter took the time to check that the skin and eye colors reported by the patients matched the real colors, although the interviewers were asked not to influence the answers. The interviewers were trained to ask the subjects for their youthful natural hair color. Differential reporting of skin phenotype is thus unlikely. Differential recall of outdoor activities is not very probable because the suspected relationship between UV radiation exposure and malignant lymphoma is not common knowledge in France and the interviewers were not aware of the hypotheses under study. Both the cases and controls may have had difficulty recalling how their skin reacted to sun exposure, but that non-differential difficulty is far less unlikely for the most sensitive subjects.

Farming was more frequent among the NHL and MM cases but, after adjustment for socioeconomic category and farming, the results were unchanged (24). Adjustment for a history of mononucleosis did not change the results (25).

Four recent large case-control studies conducted in Australia (11,18), Sweden and Denmark (19), Germany (20) and the USA (21) investigated the influence of skin type and UV radiation exposure on LM.

The Australian study (Hughes et al. (11)) found moderately but significantly increased ORs associated with very fair skin color and poor ability to tan. Those findings are consistent with the results of this study. The associations were not reported by the Swedish (Smedby et al. (19)) or US (Hartge et al. (21)) study. In the latter two studies, the controls tended to be less sensitive to the sun: 40 and 38% of the subjects reacted strongly to the first seasonal exposure, compared to 51% in the Australian study and 48% in the present study. The proportion of blond or red-haired subjects in the control group of the present study was 8%, and thus markedly less than the proportions in the Australian (23%) and Swedish (30%) studies. The proportion of subjects with very fair or fair skin color was similar in this study (69%) to that in the Australian study (75%) and markedly higher than that in the US study (41%). Between-population differences in skin phenotype may account for some of the inconsistency.

With regard to the frequency of outdoor exposure, the results of this study do not contradict those of the four previous studies, which suggest a possible, slight, protective effect of UV radiation exposure with respect to the risk of NHL and other LM. UV radiation exposure for limited durations during childhood and adulthood was negatively and significantly associated with NHL in the Australian study and with NHL and HL in the Swedish and German studies. Similar, albeit non-significant, results for chronic or intermittent UV radiation exposure were generated by the US study.

In the present study, low frequencies of outdoor leisure activity (1.5 to 5 h/week), when practiced in the last ten years, and occasional esthetic use of artificial UV radiation, were positively, but slightly and not significantly, associated with NHL, HL and LPS. Those findings could be due to chance, but may also be regarded as an indication that severe intermittent UV radiation exposure, rather than chronic exposure, might be a risk factor. Unfortunately, it was not possible to identify the severe intermittent exposures among the self declared intermittent exposures.

The initial assumption that UV radiation exposure increases the risk of NHL is supported by photoimmunologic data (3) showing that exposure to UV radiation may cause systemic T-cell immunosuppression (decrease in Th1 activity). In contrast, it has been suggested that vitamin D production could have a protective effect with respect to the risk of lymphoid malignancies (18-20). Moreover, ecological and individual studies are generating increasing evidence that some cancers (colon, prostate, breast) may be less frequent in areas with a high degree of solar radiation (22). High serum vitamin D levels may be associated with a lower risk of colorectal cancer. Vitamin D is known to inhibit cell growth and promote cell differentiation (23).

In sum, the results of this study suggest a positive association between the most reactive and palest skin types and both NHL and HL in men. The results do not rule out the hypothesis that UV radiation exposure through outdoor activities may be negatively related to LM.

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Table 1: Distribution of cases and controls by stratification variable and socioeconomic category (LM: lymphoid malignancy; NHL: non-Hodgkin's lymphoma; HL: Hodgkin's lymphoma; LPS: lymphoproliferative syndrome; MM: multiple myeloma) – ORs were estimated by unconditional logistic regression adjusted for stratification variables.

	All LM				NHL				HL				LPS				MM			
	Cases n=813	Controls n=748	Co/Ca	p	Cases n=395	Controls n=698	Co/Ca	P	Cases n=147	Controls n=415	Co/Ca	p	Cases n=168	Controls n=464	Co/Ca	p	Cases n=103	Controls n=476	Co/Ca	p
Gender				*ns*				*ns*				*ns*				*ns*				**
Female	41%	39%	0.9		39%	38%	1.7		42%	36%	2.4		38%	34%	2.5		50%	35%	3.2	
Male	59%	61%	0.9		61%	62%	1.8		58%	64%	3.1		62%	66%	2.9		50%	65%	6.0	
Center				*ns*				*				*ns*				***				*ns*
Brest	19%	19%	0.9		22%	20%	1.6		15%	18%	3.3		13%	24%	5.0		20%	23%	5.1	
Caen	14%	14%	0.9		6%	12%	3.4		11%	12%	3.2		38%	19%	1.4		10%	11%	5.4	
Nantes	19%	18%	0.9		19%	17%	1.5		27%	26%	2.7		16%	15%	2.7		12%	12%	4.8	
Lille	10%	10%	1.0		8%	9%	2.2		3%	2%	1.6		18%	14%	2.0		14%	11%	3.6	
Toulouse	17%	18%	1.0		19%	19%	1.8		22%	21%	2.8		5%	12%	6.0		19%	19%	4.6	
Bordeaux	21%	21%	0.9		26%	23%	1.5		22%	21%	2.8		10%	16%	4.7		25%	24%	4.5	
Age				*ns*				*ns*				***				*ns*				*ns*
< 30 y	9%	10%	1.0		5%	7%	2.6		37%	17%	1.3		-	-	-		-	-	-	
30-39 y	9%	10%	0.9		10%	10%	1.8		21%	15%	2.0		3%	4%	3.8		3%	3%	4.3	
40-49 y	17%	17%	0.9		18%	17%	1.7		22%	22%	2.8		13%	14%	2.9		10%	12%	5.5	
50-59 y	29%	29%	0.9		34%	30%	1.6		10%	27%	8.0		34%	32%	2.6		32%	39%	5.6	
60-69 y	26%	25%	0.9		23%	25%	2.0		10%	18%	5.0		36%	36%	2.8		43%	34%	3.7	
≥ 70 y	10%	10%	1.0		11%	10%	1.6		1%	1%	6.0		14%	14%	2.9		13%	12%	4.5	
	Cases	Controls	OR [95%CI]		Cases	Controls	OR [95%CI]		Cases	Controls	OR [95%CI]		Cases	Controls	OR [95%CI]		Cases	Controls	OR [95%CI]	
Socioeconomic category				**				*ns*				*				*ns*				*ns*
Scientific/administrative manager	23%	20%	1.1	[0.8-1.5]	22%	20%	1.1	[0.7-1.6]	25%	19%	1.4	[0.8-2.4]	23%	21%	1.1	[0.7-1.9]	23%	21%	1.2	[0.6-2.4]
Administrative, sales, service worker	26%	25%	1.0	ref.	25%	24%	1.0	ref.	30%	24%	1.0	ref.	27%	24%	1.0	ref.	24%	23%	1.0	Ref.
Factory worker	37%	44%	0.8	[0.6-1.0]	39%	45%	0.9	[0.6-1.2]	26%	45%	0.5	[0.3-0.9]	40%	45%	0.8	[0.5-1.2]	36%	45%	0.9	[0.5-1.6]
Agricultural worker	10%	6%	1.5	[1.0-2.2]	11%	7%	1.6	[1.0-2.7]	5%	6%	1.0	[0.4-2.6]	9%	8%	1.2	[0.6-1.4]	14%	8%	2.2	[1.0-5.0]
Unemployed	4%	5%			3%	4%			14%	6%			1%	2%			3%	3%		
Education				#				*ns*				#				*ns*				*ns*
Less than secondary level	65%	68%	1.0	Ref.	67%	69%	1.0	ref.	44%	62%	1.0	ref.	75%	75%	1.0	ref.	70%	73%	1.0	ref.
Secondary level	35%	32%	1.2	[1.0-1.5]	33%	31%	1.1	[0.8-1.4]	56%	38%	1.5	[1.0-2.3]	25%	25%	1.2	[0.8-1.9]	30%	27%	1.2	[0.7-2.0]

# p<0.10;* p<0.05; ** p<0.01;*** p<0.001; ns: p>0.10

Table 2: Association between skin type and lymphoid malignancy (LM) (NHL: non-Hodgkin's lymphoma; HL: Hodgkin's lymphoma; LPS: lymphoproliferative syndrome; MM: multiple myeloma) – ORs were estimated by unconditional logistic regression adjusted for stratification variables.

	All LM				NHL				HL				LPS				MM			
	Cases	Controls	OR [95%CI]		Cases	Controls	OR [95%CI]		Cases	Controls	OR [95%CI]		Cases	Controls	OR [95%CI]		Cases	Controls	OR [95%CI]	
	n=813	n=748			n=395	n=698			n=147	n=415			n=168	n=464			n=103	n=476		
Eye color																				
Blue/gray/green	398	359	1.0	[0.8-1.3]	179	334	0.9	[0.7-1.2]	69	184	1.1	[0.7-1.6]	100	238	1.3	[0.9-1.9]	50	234	1.0	[0.6-1.6]
Hazel/brown/black	412	386	1.0	ref.	215	361	1.0	ref.	78	231	1.0	ref.	67	223	1.0	ref.	52	239	1.0	ref.
Hair color																				
Blond/red	73	57	1.2	[0.8-1.7]	33	53	1.1	[0.7-1.8]	14	22	1.8	[0.8-3.8]	16	39	1.1	[0.6-2.1]	10	40	1.1	[0.5-2.3]
Light brown/ dark brown/black	738	687	1.0	ref.	362	641	1.0	ref.	132	392	1.0	ref.	151	422	1.0	ref.	93	433	1.0	ref.
Skin color																				
Very fair/fair	585	512	1.2	[0.9-1.5]	281	478	1.1	[0.8-1.5]	112	281	1.6	[1.0-2.5]	118	323	1.1	[0.7-1.7]	74	325	1.1	[0.7-1.9]
Olive/brown	224	233	1.0	ref.	113	217	1.0	ref.	35	134	1.0	ref.	48	138	1.0	ref.	28	148	1.0	ref.
Propensity to burn (skin reaction to first unprotected seasonal exposure to sun)																				
Severe/ painful burn	398	331	1.3	[1.0-1.6] *	191	311	1.2	[0.9-1.6]	74	164	1.5	[1.0-2.2]	88	205	1.4	[1.0-2.1]	45	207	1.1	[0.7-1.7]
Burn then tan/ tan without burning	405	411	1.0	ref.	198	382	1.0	ref.	73	248	1.0	ref.	79	253	1.0	ref.	55	263	1.0	ref.
Ability to tan (skin reaction to repeated exposures to sun)																				
None/mild tan	156	127	1.2	[0.9-1.5]	76	121	1.1	[0.8-1.5]	34	64	1.7	[1.0-2.8] *	30	73	1.1	[0.7-1.8]	16	80	0.9	[0.5-1.6]
Moderate/deep tan	648	617	1.0	ref.	315	573	1.0	ref.	113	350	1.0	ref.	136	387	1.0	ref.	84	392	1.0	ref.
Hair and skin profile																				
Blond/red hair + severe/painful burn	53	40	1.4	[0.9-2.1]	28	39	1.5	[0.9-2.5]	12	13	3.4	[1.4-8.4] *	8	28	0.9	[0.4-2.2]	5	27	0.9	[0.3-2.5]
Light brown/dark brown/black hair + severe/painful burn	344	290	1.3	[1.0-1.5] *	163	271	1.2	[0.9-1.6]	61	150	1.3	[0.9-2.0]	80	177	1.5	[1.0-2.2] *	40	180	1.1	[0.7-1.8]
Burn then tan/ Tan without burning	405	411	1.0	ref.	198	382	1.0	ref.	73	248	1.0	ref.	79	253	1.0	ref.	55	263	1.0	ref.
p trend				*0.03*				*0.09*				*0.02*				*0.21*				*0.87*

* p < 0.05 (p-values greater than 0.05 not shown in the table)

Table 3: Association between outdoor leisure exposures, use of artificial UV radiation and lymphoid malignancy (LM) (NHL: non-Hodgkin's lymphoma; HL: Hodgkin's lymphoma; LPS: lymphoproliferative syndrome; MM: multiple myeloma) – ORs were estimated by unconditional logistic regression adjusted for stratification variables.

	All LM				NHL				HL				LPS				MM			
	Cases	Controls	OR [95%CI]		Cases	Controls	OR [95%CI]		Cases	Controls	OR [95%CI]		Cases	Controls	OR [95%CI]		Cases	Controls	OR [95%CI]	
	n=813	n=748			n=395	n=698			n=147	n=415			n=168	n=464			n=103	n=476		
Frequency of outdoor activities since leaving school (h/week)																				
0.0-1.0	502	440	1.0	Ref.	218	410	1.0	Ref.	95	253	1.0	Ref.	98	268	1.0	Ref.	71	272	1.0	Ref.
1.0-2.5	100	99	0.9	[0.7-1.2]	52	95	0.9	[0.6-1.4]	15	47	0.9	[0.5-1.8]	23	60	1.0	[0.6-1.8]	10	66	0.6	[0.3-1.3]
2.5-6.0	94	92	0.9	[0.7-1.3]	49	89	0.9	[0.6-1.4]	15	54	0.8	[0.4-1.6]	20	59	0.9	[0.5-1.6]	10	62	0.6	[0.3-1.4]
6.0-31.5	81	88	0.8	[0.6-1.2]	42	80	0.9	[0.6-1.4]	12	47	0.7	[0.4-1.5]	19	56	0.8	[0.5-1.6]	8	57	0.5	[0.2-1.3]
p trend			ns				ns				ns				ns				#	
Frequency of outdoor activities in the preceding 10 years (h/week)																				
0.0-1.5	471	422	1.0	Ref.	223	392	1.0	Ref.	94	245	1.0	Ref.	87	255	1.0	Ref.	67	260	1.0	Ref.
1.5-3.5	80	64	1.2	[0.8-1.7]	41	62	1.2	[0.7-1.8]	10	37	1.1	[0.5-2.3]	21	40	1.7	[0.9-3.1]	8	45	0.7	[0.3-1.7]
3.5-7.5	81	72	1.0	[0.7-1.5]	49	70	1.2	[0.8-1.9]	12	31	1.4	[0.6-3.0]	13	47	0.8	[0.4-1.6]	7	50	0.5	[0.2-1.2]
7.5-52.5	63	66	0.9	[0.6-1.3]	29	63	0.8	[0.5-1.4]	6	36	0.6	[0.2-1.6]	19	48	1.1	[0.6-2.2]	9	49	0.6	[0.3-1.4]
p trend			ns				ns				ns				ns				#	
Esthetic use of artificial UV radiation																				
No	768	707	1.0	Ref.	381	661	1.0	Ref.	135	393	1.0	Ref.	156	442	1.0	Ref.	96	455	1.0	Ref.
Yes	42	38	1.1	[0.7-1.7]	14	34	0.8	[0.4-1.5]	12	22	1.6	[0.7-3.6]	11	19	1.5	[0.7-3.5]	5	18	1.2	[0.4-3.6]
Regularly	7	13	0.5	[0.2-1.3]	2	11	0.3	[0.1-1.5]	2	8	0.6	[0.1-3.3]	*2*	*6*	0.9	[0.2-4.6]	1	6	0.8	[0.1-7.3]
Occasionally	35	25	1.4	[0.8-2.3]	12	23	1.0	[0.5-2.1]	10	14	2.2	[0.9-5.5]	9	13	1.9	[0.7-4.7]	4	12	1.4	[0.4-4.9]
Medical use of artificial UV radiation																				
No	796	738	1.0	Ref.	387	688	1.0	Ref.	143	410	1.0	Ref.	166	456	1.0	Ref.	100	469	1.0	Ref.
Yes	14	7	1.8	[0.7-4.5]	8	7	2.0	[0.7-5.7]	4	5	3.2	[0.8-13.2]	1	5	0.4	[0.1-3.9]	1	4	0.9	[0.1-8.7]
All uses of artificial UV radiation																				
No	757	700	1.0	Ref.	374	654	1.0	Ref.	133	388	1.0	Ref.	155	437	1.0	Ref.	95	451	1.0	Ref.
Yes	53	45	1.1	[0.7-1.7]	21	41	1.0	[0.5-1.7]	14	27	1.5	[0.7-3.2]	12	24	1.3	[0.6-2.7]	6	22	1.2	[0.4-3.1]

# p<0.10; ns: p>0.10